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SOUTHERN DISTRICT OF CALIFORNIA

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UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF CALIFORNIA

GEN-PROBE, INCORPORATED,

Plaintiff,

v.

VYSIS, INC.,

Defendant.

CASE NO. 99CV 2668H (AJB)

**DECLARATION OF DR. DAVID H.
PERSING IN SUPPORT OF VYSIS'
OPPOSITION TO GEN-PROBE'S
MOTION FOR PARTIAL SUMMARY
JUDGMENT**

Date: June 8, 2001

Time: 10:30 a.m.

Dept.: Courtroom 1

I, David H. Persing, declare as follows:

1. I have personal knowledge of the facts set forth herein, and if called as a witness
would testify to the truth thereof.

2. I am presently Vice President, Molecular Biology, at Corixa Corporation, and
Medical Director, Infectious Disease Research Institute, both in Seattle, Washington. I received a
Ph.D. (Department of Biochemistry and Biophysics) and an M.D. (School of Medicine) from the

1 University of California, San Francisco in 1988. My Ph.D. work was performed in the laboratory of
2 Nobel laureate Harold Varmus. I was a Resident and Research Fellow at the Yale School of
3 Medicine from 1988-1990. I was employed by the Mayo Clinic, Rochester, Minnesota from 1990 to
4 1999. My work has been primarily directed to the study of infectious diseases, including study of the
5 application of nucleic acid hybridization assays in medical diagnostics. I was director from 1993 to
6 1999 of the Molecular Microbiology Lab of the Mayo Clinic, which was one of the premier centers
7 for the diagnosis of infectious diseases by molecular methods. There, I pioneered techniques for
8 pathogen discovery and contamination control, and discovered several new pathogens. I am a
9 member of three Scientific Advisory Boards, including the Scientific Advisory Board of Vysis, Inc.,
10 and am an Editor-in-Chief of the reference text Diagnostic Molecular Microbiology PRINCIPLES
11 AND APPLICATIONS. A list of my patents and scientific publications is included in my
12 curriculum vitae attached as Exhibit A.

13 3. I have extensive experience in the fields of nucleic acid hybridization and
14 amplification. I have been familiar with and been a practitioner of nucleic acid hybridization assays
15 and various amplification techniques used with nucleic acid hybridization assays since about 1985.
16 As indicated in Exhibit A, I have a number of scientific publications relating to these techniques.

17 4. I have been retained as an expert by Vysis in this lawsuit. In that regard, I have
18 reviewed the claims, specification, and pertinent prosecution history of U.S. Patent No. 5,750,338
19 ("338 patent"). My involvement in the patent application that became the '338 patent goes back to
20 1997 when I submitted a declaration to the United States Patent & Trademark Office relating to the
21 unobviousness of the combination of target capture prior to amplification as disclosed and claimed
22 by the '338 patent. A copy of my July 9, 1997 Declaration is attached hereto as Exhibit B.

23 5. The '338 patent discloses and claims a method for detecting a target nucleic acid
24 (polynucleotide) in a sample by performing target capture and then amplifying the target nucleic
25 acid. Target capture is a procedure involving binding (hybridizing) a target nucleic acid in a sample
26 to a support and separating the bound target from the sample. Amplification is an *in vitro* technique
27 for making multiple copies of the target nucleic acid to enable the target nucleic acid to be detected.
28 By targeting a portion of the nucleic acid of an organism such as a virus or bacterium, for example,

1 the method of the '338 patent enables the presence of the target organism to be detected in a sample
2 such as blood, even if the organism is present in very small amounts. Among other advantages,
3 target capture purifies the sample by removing non-target materials such as contaminants and
4 inhibitors that can interfere with the amplification step. By separating the target from the sample
5 prior to amplification, the invention of the '338 patent enables effective removal of these
6 contaminants and inhibitors from the system enabling amplification to proceed optimally.

7 6. I have read the Declaration of Dr. Joseph Falkinham In Support of Gen-Probe's
8 Motion For Partial Summary Judgment and disagree with the conclusions presented in paragraphs 5
9 and 52 of that Declaration. Specifically, I disagree with Dr. Falkinham's conclusions that as of
10 December 21, 1987, a person of ordinary skill in the art (a) would have understood the term
11 "amplifying" as used in the claims of the '338 patent to mean amplifying any nucleic acid sequence
12 present in the sample only by the use of non-specific amplification methods described in the '338
13 patent, and (b) would not have understood the term "amplifying" to mean amplifying by use of
14 sequence-specific amplification methods.

15 7. For the reasons pointed out below, it is my opinion from my review of the '338 patent
16 claims, specification, and prosecution history that those of ordinary skill in the art in December 21,
17 1987 would have understood the term "amplifying" in the claims of the '338 patent to include
18 specific types of amplification methods, and would not have understood that term as used in the
19 patent to be limited to non-specific types of amplification methods.

20 8. First of all, there is nothing from the context of the '338 patent specification that
21 would have led those of ordinary skill in the art in December of 1987 to believe that the inventors
22 meant to limit their invention to non-specific types of amplification. Performing non-specific
23 amplification after target capture would have been a much more challenging approach to molecular
24 diagnostics in 1987 than performing specific amplification after target capture. That is because non-
25 specific amplification techniques amplify all of the nucleic acid in a sample, both target and non-
26 target nucleic acid. Specific amplification techniques, in contrast, are intended to amplify only the
27 target nucleic acid. Thus, if target capture could be shown to purify the target nucleic acid in a
28 sample sufficiently so that non-specific amplification would allow detection of the target nucleic acid

1 with the attendant benefits discussed above in paragraph 5, then those of ordinary skill in the art in
2 December 1987 would have certainly understood that target capture followed by specific
3 amplification would also successfully do so to achieve these same benefits.

4 9. In addition, in my opinion the particular language used in the '338 patent specification
5 would not have indicated to those of ordinary skill in this field that the inventors wanted to exclude
6 specific amplification from the invention. It is my understanding that the '338 patent application was
7 a continuation-in-part application of an earlier application that was directed only to target capture
8 techniques. The primary discussion of the invention of combining target capture with amplification
9 begins at column 30, line 15 of the '338 patent. The first sentence defines the invention broadly by
10 stating that "[t]he sensitivity of the above DNA or RNA target capture methods can be enhanced by
11 **amplifying** the captured nucleic acids." (Emphasis added.) The specification then describes a
12 particular benefit of the invention, that "[t]his **can be** achieved by non-specific replication using
13 standard enzymes" (Emphasis added.) It is important to note that the specification does **not** say
14 that enhanced sensitivity of the target capture methods **is** achieved by non-specific amplification, but
15 rather it says that it **can be** achieved by non-specific amplification. In so stating, the specification
16 sets a minimum requirement for amplification specificity, but does not indicate that more specific
17 amplification methods should be excluded.

18 10. The specification then again describes the invention as including amplification
19 generally in the paragraph at column 30, lines 23-29. The paragraph following this describes both
20 specific and non-specific amplification, but points out the particular benefits of the invention when
21 using non-specific amplification:

22 Amplification of the target nucleic acid sequences, because it follows purification of
23 the target sequences, **can** employ non-specific enzymes or primers (i.e. enzymes or
24 primers which are capable of causing the replication of virtually any nucleic acid
25 sequence). Although any background, non-target, nucleic acids are replicated along
26 with target, this is not a problem because most of the background nucleic acids have
27 been removed in the course of the capture process. Thus **no specially tailored**
28 **primers are needed** for each test, and the same standard amplification reagents can
be used, regardless of the targets.

Col. 30, lines 30-40, emphasis added.

1 11. The paragraph quoted above points out that the use of target capture in accordance
2 with the invention makes it possible to use non-specific primers (i.e., non-specific amplification).
3 Without the use of target capture prior to amplification, non-specific amplification would not be a
4 viable technique for detecting target nucleic acids in a sample because, as pointed out in the quoted
5 paragraph, non-specific amplification causes the replication of virtually any nucleic acid sequence,
6 including other irrelevant nucleic acids in the sample. However, because the invention of the '338
7 patent provides a target capture step that removes background, non-target nucleic acids from the
8 sample prior to amplification, this is not a problem. The specification thus points out that no
9 specially tailored primers (used in specific amplification) are **needed** for each test. The specification
10 does not state that one would not want to use specially tailored primers, only that such primers are
11 not needed in this invention. Thus, an important advantage of the invention is that, because of the
12 preceding target capture step, either specific or non-specific amplification can be successfully used in
13 nucleic acid detection assays; whereas without the invention, only specific amplification could be
14 used.

15 12. The disclosure at column 30, lines 15-40 of the '338 patent specification tells me and
16 those of ordinary skill in the art that while the use of target capture made it possible to use non-
17 specific amplification in assays for detecting nucleic acids, the invention was more generally directed
18 to the use of target capture prior to either specific or non-specific amplification. The benefits of the
19 invention, i.e., purifying the sample by removing non-target materials such as contaminants and
20 inhibitors that can interfere with the amplification step, would be obtained with both specific and
21 non-specific amplification, especially since it is now widely recognized that even the most specific
22 amplification methods comprise a degree of non-specificity. If the inventors had wanted to limit the
23 invention to non-specific amplification, I believe they would not have drafted the text of the
24 application as they did.

25 13. I also disagree with Dr. Falkinham's statements in his declaration that "the primers
26 described in the ['338] patent are not pre-selected to bind to specific nucleotide sequences as part of
27 the amplification process" and that Example 5 describes only non-specific amplification. See
28 paragraphs 14 and 31, respectively. To the contrary, Example 5 of the '338 patent does disclose the

1 use of a specific primer. In particular, while Example 5 states initially that random oligohexamer
2 primers can be used to achieve non-specific amplification, Example 5 also discloses that
3 "[a]lternatively, the double stranded DNA can be formed by synthesis starting from capture probe a."
4 Col. 31, lines 48-49. In this instance, the capture probe acts as the primer. Since the capture probe
5 binds specifically to the target DNA, the capture probe would be a specific primer to the target. This
6 is an example of specific amplification because the primer, capture probe a, binds to a specific,
7 unique DNA sequence in the target organism.

8 14. I have also reviewed the prosecution history of the '338 patent. In my opinion, the
9 correspondence between the applicants for the '338 patent and the Patent Office leads to the
10 inescapable conclusion that both the applicants and the Patent Office (no fewer than five different
11 Patent Office Examiners) considered the claimed invention to encompass the polymerase chain
12 reaction ("PCR"), which is a type of specific amplification.

13 15. Patent Examiner Scott A. Chambers, Ph.D, and Primary Patent Examiner Amelia
14 Burgess Yarbrough cited the basic Mullis PCR patents in rejecting the claims of the '338 patent
15 application in the first Official Action by the Patent Office. July 20, 1990 Office Action (Paper No.
16 2) in application serial no. 07/136,920, pages 3-4. Clearly, if the Patent Examiners had believed that
17 the claims of the '338 patent application were limited to non-specific amplification, it would have
18 been illogical for them to have cited the PCR patents against the application, because PCR is a type
19 of specific amplification. Then, Examiner Chambers and Primary Examiner Margaret Moskowitz
20 continued to cite the Mullis PCR patents against the pending patent claims. March 12, 1992 Office
21 Action (Paper No. 2) in application serial no. 07/644,967, page 3; November 5, 1992 Office Action
22 (Paper No. 3) in application serial no. 07/944,505, page 3. In responding to rejections of the pending
23 claims based on the Mullis PCR patents, the owner of the '338 patent never attempted to distinguish
24 the Mullis patents by arguing that Mullis disclosed specific amplification, whereas the invention of
25 the '338 patent was directed to non-specific amplification. To the contrary, the patent owners
26 repeatedly emphasized that the invention included PCR-type amplification:

27 Applicants' invention principally serves to enhance the sensitivity of nucleic acid
28 hybridization assays utilizing target amplification. **Targets can be amplified by
a number of ways including PCR.** Applicant's invention enhances sensitivity

1 by eliminating from the amplification medium extraneous (nonspecific) nucleic
2 acids which might otherwise be amplified by PCR thereby introducing noise into
the assay.

3 Page 18 of December 5, 1995 Preliminary Amendment and Response to Restriction Requirement
4 (Paper No. 8) (responding to November 5, 1992 Office Action in application serial no. 07/944,505),
5 page 18, emphasis added.

6 16. If the patent owner had considered the invention to be limited to non-specific types of
7 amplification, I believe it would have argued this to the Patent Office to overcome the rejection of
8 the patent claims over the Mullis PCR patents. Instead, the patent owner maintained all along that
9 the invention encompassed PCR and argued that the invention was not obvious in view of the PCR
10 patents.

11 17. In fact, the owner of the '338 patent was able to obtain allowance of the patent claims
12 by convincing the Patent Office, *inter alia*, that the invention of including a target capture step to
13 purify a sample prior to PCR amplification would not have been obvious to those of ordinary skill in
14 the art as of the filing date of the original application. Patent Examiner Dianne Rees, Ph.D., and
15 Primary Patent Examiner W. Gary Jones make it clear in the very first sentence of their Examiner's
16 Statement of Reasons for Allowance that these Examiners considered the claims of the '338 patent to
17 encompass specific amplification techniques such as PCR:

18 The claims are drawn to methods of **PCR amplification** wherein the target is first
19 separated from the sample by using a support that binds to the target
polynucleotide and then amplified.

20 Page 2 of October 16, 1997 Notice of Allowability (Paper No. 23), emphasis added.

21 18. In my opinion, the only reasonable conclusion one can reach after reading the
22 prosecution history of the '338 patent is that both the applicants for the '338 patent and the five
23 patent examiners who examined the patent application believed that the term "amplify" in the patent
24 claims included specific amplification.

25 19. In my opinion, for the reasons pointed out above, those of ordinary skill in the art as
26 of December 21, 1987 reading the specification of the '338 patent would conclude that the term
27 "amplify" as used in the claims of the '338 patent includes specific amplification. It is also my
28 opinion from my review of the prosecution history of the '338 patent that both the applicants and the

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1 patent examiners considered the invention to encompass specific amplification techniques such as
2 PCR. For these reasons as well as the fact that the claims simply recite the term "amplify," I believe
3 the '338 patent claims include specific types of amplification.
4

5 I hereby declare under penalty of perjury under the laws of the United States of America that
6 all statements made herein of my own knowledge are true and that all statements made on
7 information and belief are believed to be true. This declaration was executed by me on this 25th day
8 of May, 2001 at Seattle, Washington.
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David H. Persing

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